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EXAMINER	
DUFFY, BRADLEY	

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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,090	LANG ET AL.	
	Examiner	Art Unit	
	BRADLEY DUFFY	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Exhibit A*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on October 6, 2008, has been entered.

2. The amendment filed October 6, 2008, is acknowledged and has been entered. Claims 10, 14 and 15 have been amended. Claim 17 has been canceled.

3. Claims 10-16 are pending in the application and are under examination.

Grounds of Rejection Withdrawn

4. Applicant's amendment filed October 6, 2008, has obviated or rendered moot the grounds of rejection set forth in the previous Office action mailed July 1, 2008.

Response to Arguments

5. While Applicant's remarks regarding the previous grounds of rejection set forth in the Office action mailed August 9, 2007 are acknowledged, they are moot in view of the 35 U.S.C. 103(a) rejections set forth hereinbelow.

Grounds of Objection

Claim Objections

6. Claims 10-16 are objected to for reciting "a polypeptide consisting of SEQ ID NO:2" in claims 10, 14 and 15. In this case, it is unconventional in the art to say that a

polypeptide consists of a SEQ ID NO, because a SEQ ID NO is actually a description of an amino acid sequence. This objection would be obviated, e.g., by amending the claims to recite "a polypeptide consisting of the amino acid sequence of SEQ ID NO:2".

Appropriate correction is required.

Specification

7. The disclosure is objected to because of the following informalities:

(a) The specification is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

Examples of such impermissible disclosures appears in the specification at, for example, page 31, line 20 and page 31, line 21.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

(b) The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Appropriate correction is required.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

> art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, because the specification, **while being enabling for making and using** a composition comprising a conjugate comprising a polypeptide consisting of SEQ ID NO:2 and a constituent or constituents selected from the group consisting of: (1) a single poly(ethylene glycol) group having an overall molecular weight of from about 30 to about 40 kDa, and (2) two poly(ethylene glycol) groups having an overall molecular weight of from about 30 to about 40 kDa and **while being enabling for making and using** any compositions encompassed by the claim, which are taught or suggested by the prior art, **does not reasonably provide enablement for using** the claimed compositions with the intended use as a pharmaceutical. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

MPEP § 2164.01 states:

> The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue". These factors, which have been outlined in the Federal Circuit decision of *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), include, but are not limited to, the nature of the invention, the state of the prior art, the relative skill of those in the

art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed. See also *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

The amount of guidance, direction, and exemplification disclosed in the specification, as filed, would not be sufficient to enable the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

The claims are herein drawn to pharmaceutical compositions comprising conjugates comprising a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and a constituent or constituents selected from the group consisting of: (1) a single poly(ethylene glycol) group having an overall molecular weight of from about 30 to about 40 kDa, and (2) two poly(ethylene glycol) groups having an overall molecular weight of from about 30 to about 40 kDa.

In this case, wherein claim 16 is drawn to using the recited compositions with a pharmaceutical intended use, it is submitted that the specification does not enable compositions comprising a conjugate comprising an insulin-like growth factor binding protein 4 polypeptide consisting of SEQ ID NO:2 and poly(ethylene glycol) for use pharmaceutically. For example, the specification only provides *in vitro* evidence that conjugates consisting of a of polypeptide with the amino acid sequence of the human insulin-like growth factor binding protein 4 polypeptide, i.e., SEQ ID NO:2, and one or two poly(ethylene glycol) group(s), said poly(ethylene glycol) group(s) having an overall molecular weight of from about 30 to 40 kDa inhibit the proliferation of certain tumor cell lines in culture (see Example 12 at page 26 of the specification). Notably, the specification further teaches that of the conjugates that inhibit tumor cell line growth *in vitro,* only the conjugate designated mono40kDa-PEG-IGFBP-4 functions to inhibit tumor cell growth in a mouse xenograft model for pancreatic cancer at a high dose of 1 mg of protein per day wherein the xenograft tumor had only been introduced 7 days prior to treatment (see Example 14 staring on page 28 of the specification). Therefore,

one of skill in the art would be subject to undue experimentation to use any conjugate encompassed by the claims pharmaceutically, for example, to treat patients with established cancers.

In support of this conclusion, the state of the art was such that those of skill in the art readily recognized the unpredictability of extrapolating *in vitro* cell line data or mouse xenograft model data to treatment of a patient with an established cancer, even when the extrapolation was from the same product tested *in vitro* or in the mouse tumor model to its use as a pharmaceutical treatment in patients. With particular regard to anticancer drug discovery, Gura (*Science*. 1997; **278**: 1041-1042, of record), for example, teaches that researchers are faced with the problem of sifting through potential anticancer agents to find ones promising enough to make clinical trials worthwhile (abstract). Because of a lack of predictability, Gura discloses that often researchers merely succeed in developing a therapeutic agent that is useful for treating the cell that has been used as a model, but which is ineffective in patients, and indicates that the results acquired during pre-clinical studies are often non-correlative with the results acquired during clinical trials (page 1041, column 2). Additionally, Zips et al (in vivo, 19:1-7, 2005, of record) teach that "[u]nlike the situation *in vitro*, a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells", so predicting the effect of an anticancer agent *in vivo* based on *in vitro* data is not reliable (see page 3, right column). Additionally, Dennis (Nature, 442:739-741, August 2006, of record) states "human cells are likely to behave differently in a mouse than in a human body, making results hard to interpret) (see page 739, middle column) and that "interactions between tumour cells and their neighbors are often lost in xenografts, because proteins from one species can't interact with their counterparts in the host" (see page 740, third column). Furthermore, Srivastava (Nature Immunology, 1(5):363-366, November 2000, of record) teaches that "the human cancers that we aim to treat are well established and have taken their time getting there", while the mouse models used are often "established for anything from a few hours to less than a week before treatment" and that mouse models "must show some semblance to the human disease to be credible" (see page 365, right column). Thus, since the specification does not

provide any specific non-general guidance as to how to use the claimed conjugates pharmaceutically to treat patients with established cancer, one of skill in the art would be subject to undue experimentation to determine if such conjugates would be effective to treat patients with established cancer.

Notably, since it is highly unpredictable in the art to extrapolate mouse xenograft cancer model data to cancer treatments of established tumors, one of skill in the art would be subject to undue experimentation to use the claimed conjugates as a pharmaceutical composition to treat such established tumors as the instant specification only provides evidence that the conjugate designated mono40kDa-PEG-IGFBP-4 functions to inhibit tumor cell growth in a mouse xenograft model for pancreatic cancer.

As additional support of this conclusion, the state of the art was such that those of skill in the art readily recognized that it was highly unpredictable whether even the mono40kDa-PEG-IGFBP-4 conjugate could be used as a therapeutic intervention in patients. For example, while a conjugate comprising the human insulin-like growth factor binding protein 1 polypeptide and PEG was known to inhibit tumor cell proliferation *in vitro,* US 2005/0033035 A1 (Beisel et al, 2005, of record) teaches that only very high doses of this conjugate result in tumor growth inhibition *in vivo* (see entire document, e.g., page 2, paragraph [0009]). Thus, Beisel et al conclude that "the inhibitory effects of the PEGylated IGFBP-1 is still not sufficient for therapeutic intervention in humans because only partial response is observed even if PEGylated IGFBP-1 is given in doses of 1 mg/dose daily in mice. This corresponds to a dose of 50 mg/kgxday which can not be administered to humans by established procedures and can not be produced economically" (see page 2, paragraph [0009]). Furthermore, Van Den Berg et al (Eur. J. Can., 33(7):1108-1113, 1997, IDS file 2/2/2006) teach that after 30 days of administering PEGylated IGFBP-1 in doses of 1 mg/dose daily to mice with xenograft MDA-MB-231 tumors that tumor volume had a geometric mean of 1737 mm^3 in treated mine while control mice had a tumor volume of 3108 mm^3 (see entire document, e.g., page 111, right column and figure 2b) Notably, the specification teaches at page 28 that the mono40kDa-PEG-IGFBP-4 conjugate was administered at 1 mg/dose daily in mice and that the tumor volume had a mean of 163 mm^3 in treated

mine while control mice had a tumor volume of 226 mm^3. Therefore, as the mono40kDa-PEG-IGFBP-4 conjugate taught in the specification also only shows a partial response in the mouse xenograft model in which it was tested and because it was administered at a high dose similar to the dose used in the PEGylated IGFBP-1 example, one of skill in the art would be subject to undue experimentation to use the recited mono40kDa-PEG-IGFBP-4 conjugate with the intended use as a pharmaceutical because the conjugate would have to be administered at such a high concentration that established procedures could not be used to administer it and because established procedures could not be used to make it economically. Notably, the specification does not provide any specific non-guidance guidance on any procedures that would allow the administration of the high doses required to achieve a therapeutic effect nor does it provide any specific non-guidance guidance on how to make such quantities of conjugate economically.

In view of the evidence of the lack of the predictability of the art to which the invention pertains, the lack of guidance and direction providing a specific and detailed description in applicant's specification of how to effectively use the claimed pharmaceutical compositions, undue experimentation would be required to practice the full scope of the claimed invention.

Applicant is reminded that reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

In deciding *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. "Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention." *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CA FC 1997).

Therefore, in conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with the Federal

Circuit decision of *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the amount of guidance, direction, and exemplification disclosed in the specification, as filed, is not deemed sufficient to have enabled the skilled artisan to make and/or use the claimed invention at the time the application was filed without undue and/or unreasonable experimentation.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 10 and 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/73452 A2 (Ashkenazi et al, 2000), in view of WO 1994/22466 A1 (Cox et al, 1994, IDS filed February 2, 2006), Francis et al (Int. J. Hem., 68:1-18, 1998, IDS filed 2/2/2006), and Byun et al (J. End., 169:135-143, 2001, IDS filed 2/2/2006).

The claims are herein drawn to conjugates comprising a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and one or two poly(ethylene glycol) group(s), said poly(ethylene glycol) group(s) having an overall molecular weight of from about 30 to 40 kDa and a composition comprising such a conjugate and a pharmaceutically acceptable carrier. Claim 14 further recites that the poly(ethylene glycol) (PEG) groups are linked to cysteine 110 and/or cysteine 117 of the polypeptide consisting of the amino acid sequence of SEQ ID NO:2. Claim 15 further recites that the poly(ethylene glycol) is bound to primary amino groups or thiol i.e., cysteine groups.

While, the specification does not expressly define poly(ethylene glycol) group(s) having an overall molecular weight of from about 30 to 40 kDa, the breadth of the claims is interpreted in light of the disclosure at page 7, lines 6-8 that states, "It is obvious to a person skilled in the art that small deviations from this range of molecular weight are possible". Furthermore at page 7, lines 16-19, the specification discloses: "As used herein, "molecular weight" means the mean molecular weight of the PEG. The term "about" before a designated molecular weight indicates that in said PEG preparations, some molecules will weigh more and some less than the stated molecular weight". Then, at page 7, lines 24-25, the specification expressly teaches that a PEG group of about 20 kDa is exemplary of the groups contemplated for use in a conjugate and teaches at page 29 a conjugate of insulin-like growth factor binding protein 4 and PEG referred to as mono20kDa-PEG-IGFBP-4.

Ashkenazi et al teach a polypeptide designated "PRO861" that is alternatively designated "insulin-like growth factor binding protein 4" (IGFBP-4) which consists of the amino acid sequence of SEQ ID NO:59 that has a signal sequence over residues 1-21(see entire document, e.g., page 94 and Figure 24), which after removal of the signal sequence consists of the instantly recited amino acid sequence of SEQ ID NO:2 (see

attached exhibit A). Ashkenazi et al further teach making the polypeptides of the invention without the signal sequence and conjugating the polypeptides of the invention with poly(ethylene glycol) (see e.g., pages 20 and 54). Finally at page 114-116 Cox et al teach purifying the polypeptides of the invention in aqueous compositions, which inherently comprise a pharmaceutically acceptable carrier, such as water.

However, Ashkenazi et al do not expressly teach conjugating one or two poly(ethylene glycol) group(s), wherein said poly(ethylene glycol) group(s) have an overall molecular weight of from about 30 to 40 kDa to polypeptides or methods of conjugating poly(ethylene glycol) group(s) to polypeptides.

These deficiencies are made up for in the teachings of Cox et al, Francis et al, and Byun et al.

Cox et al teach conjugating insulin-like growth factor binding proteins (IGFBPs) to polyethylene glycol (PEG) to increase the circulating half life of the protein, as increasing the molecular weight of a protein by conjugating polyethylene glycol to the protein is known in the art to increase the serum half life of the protein in circulation (see entire document, e.g., pages 11 and 12). Furthermore, at page 9, Cox et al teach that the term "IGFBP" i.e., insulin-like growth factor binding protein refers to any of the six known IGF binding proteins. Then at page 46 Cox et al teach methods of PEGylating[1] an IGFBP-1 polypeptide at cysteine thiol groups at positions 98 and/or 101 with monomethyoxy-PEG with an average molecular weight of 20 kDa by methods that partially reduce the disulfide bonds in the protein to create free thiol groups. Cox et al further teach at page 54 that such PEGylated IGFBP-1 polypeptides have an increased circulating serum half-life because of decreased plasma clearance. Finally at page 13 Cox et al teach said IGFBPs in compositions comprising pharmaceutically acceptable carriers.

Francis et al teach that polyethylene glycol modification methods are well-established techniques for the modification of potentially therapeutic proteins and that, at the time, this class of pharmaceuticals contained 8 of the world's top 100 drugs in

terms of sales (see entire document, e.g., page 2, left column). Francis et al teach that there are at least 8 advantages to PEGylating proteins including, increased serum circulation time, reduced antigenicity, improved solubility, resistance to proteolysis, improved bioavailability, reduced toxicity, improved thermal and mechanical stability and easier formulation (e.g., page 2, left and right column). Francis et al further teach that there is a correlation between increased circulation time of a polypeptide and larger PEG molecules. Francis et al further teach methods of PEGylating proteins which results in proteins that are PEGylated at primary amino groups or free thiol groups (e.g., page 5, left column).

Byun et al teach that IGFBP-4 is known to inhibit (insulin-like growth factors) IGFs *in vitro* and *in vivo* and that IGFBP-4 is unique compared to the other five IGFBPs because its central region comprises cysteines at amino acid 110 and 117, while the other IGFBPs lack cysteines in this region (see entire document, e.g., page 135, left column, page 142, right column and page 139, figure 2). Byun et al further teach that IGFBP-4 analogs lacking the central region comprising cysteines at amino acid 110 and 117 have similar IGF-I and IGF-II binding activity compared to the IGFBP-4 protein with this region and, for this reason, it is not thought that these residues are important for the activity of the protein (see e.g., page 142, right column).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to PEGylate the polypeptide consisting of the amino acid sequence of SEQ ID NO:2, as taught by Ashkenazi et al, with one or two poly(ethylene glycol) group(s), said poly(ethylene glycol) group(s) having an overall molecular weight of from about 30 to 40 kDa, by the methods of Cox et al and/or Francis et al because Cox et al teach that the PEGylation of another protein in the IGFBP family, i.e., IGFBP-1 increased its circulating half-life and suggests that doing so would be expected to similarly increase the circulating half-life of any of the other IGFBP polypeptides. Accordingly, one of skill in the art would have been motivated to make

[1] The art commonly uses the term PEGylate to describe processes of conjugating PEG to proteins (see e.g., abstract of Francis et al)

conjugates of a polypeptide consisting of the amino acid sequence of SEQ ID NO:2, with one or two poly(ethylene glycol) group(s), said poly(ethylene glycol) group(s) having an overall molecular weight of from about 30 to 40 kDa conjugated to primary amine groups or thiol, i.e., free cysteines groups, because such conjugates were known in the art to be able to increase the circulating half-life of other proteins, including one in the same family, i.e., IGFBP-4 and because, as evidenced by Francis et al, there are many advantages to PEGylating proteins for their development as a potential therapeutic agent.

Furthermore, as Cox et al teach conjugating IGFBP-1 by a method that partially reduces disulfide bonds to create free thiol groups at cysteine thiol residues which were added by mutation to the central region of the IGFBP-1 protein, to conjugate one or two polyethylene glycol groups with an average molecular weight of 20 kDa to the protein, and because Byun et al teach that IGFBP-4 naturally contains 2 cysteines in the central region that do not appear to be important for activity of the IGFBP-4 protein, one of skill in the art would have been further motivated to use the methods disclosed by Cox et al to create free thiol groups in the IGFBP-4 protein of Ashkenazi et al that could be PEGylated by either of the methods of Cox or Francis because they would have expected that using the methods of Cox to PEGylate a polypeptide IGFBP-4 consisting of the amino acids sequence of SEQ ID NO:2 would result in an active protein. Therefore, while none of the references expressly recite linking cysteines at amino acid 110 and 117 in the polypeptide consisting of the amino acid sequence of SEQ ID NO:2 with polyethylene glycol, as recited in claim 14, it is submitted that PEGylating the polypeptide consisting of the amino acid sequence of SEQ ID NO:2 by the methods of Cox et al would produce a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 that is inherently PEGylated at one or both of these residues. Notably, the methods disclosed by Cox et al to PEGylate IGFBP polypeptides comprise steps that are materially and manipulatively indistinguishable from the method disclosed in the instant specification at page 20, which also partially reduces the IGFBP-4 polypeptide to create free thiol groups, before conjugation with PEG, and which results in PEGylation at residues 110 and/or 117 in IGFBP-4 (see also page 21 of the instant specification).

Therefore, absent a showing of any difference, it is submitted that by PEGylating the polypeptide consisting of the amino acid sequence of SEQ ID NO:2 taught by Ashkenazi by the methods of Cox, one of skill in the art would obtain a conjugate structurally and materially indistinguishable from conjugates encompassed by claim 14. Furthermore, as both Cox et al and the instant specification teach that PEG preparations are heterogeneous for PEG molecules of different molecular weights, the average molecular weight of 20 kDa taught by Cox et al is also deemed to overlap with PEG molecules having an overall molecular weight of from about 30 to 40 kDa.

Finally, as multiple methods of PEGylating proteins have been described in the art as evidenced by Cox et al and Francis et al, it is apparent that one of skill in the art would have had a reasonable expectation of success in making conjugates encompassed by the scope of the claims comprising a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and one or two poly(ethylene glycol) group(s), said poly(ethylene glycol) group(s) bound to primary amino groups or thiol groups, wherein the one or two poly(ethylene glycol) group(s) have an overall molecular weight of from about 30 to 40 kDa and a composition comprising such a conjugate and a pharmaceutically acceptable carrier, such as water, *or* a conjugate comprising a polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and one or two poly(ethylene glycol) group(s), wherein the one or two poly(ethylene glycol) group(s) have an overall molecular weight of from about 30 to 40 kDa, and wherein the poly(ethylene glycol) groups are linked to cysteine 110 and/or cysteine 117 of the polypeptide consisting of the amino acid sequence of SEQ ID NO:2, in view of these references.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

13. Claims 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00/73452 A2 (Ashkenazi et al, 2000), in view of WO 1994/22466 A1 (Cox et al, 1994, IDS filed February 2, 2006), Francis et al (Int. J. Hem., 68:1-18, 1998, IDS filed

2/2/2006), and Byun et al (J. End., 169:135-143, 2001, IDS filed 2/2/2006), as applied to claims 10 and 14-16 above, and further in view of Veronese et al (Biomaterials, 22:405-417, 2001, IDS filed February 2, 2006).

Claims 11-13 are further drawn to the conjugate of claim 10, wherein one or two of the polyethylene glycol groups is a branched polyethylene glycol group.

Ashkenazi et al, Cox et al, Francis et al, and Byun et al teach this which is set forth in the above rejection of claims 10 and 14-16.

However, none of the recited references explicitly teach conjugates comprising branched polyethylene glycol groups. This deficiency is made up for in the teachings of Veronese.

Veronese et al teach methods of PEGylating proteins, with multiple different species of PEG polymer, including branched PEG groups (see entire document, e.g., page 408, left column). Furthermore, Veronese et al teach that branched PEG groups have multiple advantages over linear PEG groups, including higher retention in blood, lower immunogenicity and decreased inactivation of the proteins activity (See page 408, Figure 5 and page 412, Figure 14).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to PEGylate the IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 of Ashkenazi et al with branched PEG groups instead of the linear PEG groups of Cox et al or Francis et al to make a conjugate comprising a PEGylated IGFBP-4 polypeptide consisting of the amino acid sequence of SEQ ID NO:2 and one or two branched PEG groups having an overall molecular weight of about 30 kDa to 40 kDa.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to do so because branched PEG groups have advantages over linear PEG groups as taught by Veronese. Therefore, one of skill in the art would have been motivated to make such conjugates containing branched PEG groups to obtain the predicable advantages of the branched PEG groups taught by Veronese and would have a reasonable expectation of

success in making such conjugates as all the components of such conjugates were available and known in the art.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

14. No claims are allowed.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. US Patent No. 6,004,775 (Shimasaki et al, 1999, of record) teaches a polypeptide that is 100% identical to SEQ ID NO: 2. US 2002/0177227 A1 (Kraus et al, 2002) teach a polypeptide that is 100% identical to SEQ ID NO:2 and conjugating the polypeptides of the invention with polyethylene glycol. US Patent No. 5,212,074 (Kiefer et al, 1993) teaches a polypeptide that is 100% identical to SEQ ID NO: 2. Damon et al (Endocrinology,139:3456-3464, 1998, IDS filed February 2, 2006) teach increasing serum levels of IGFBP4 *in vivo* in a mouse prostate cancer xenograft model delays prostate tumor formation. Miyakoshi et al (Endocrinology, 142(8)3456-3464, IDS filed 02/02/2006) teach an insulin-like growth factor binding protein 4 that increases IGF bioavailability in vivo. Reddy et al (ADDR, 54:571-586, 2002, of record), teach that it is routine to optimize the PEG polymer conjugated to a polypeptide based on size and type of polymer. US Patent No. 6,207,640 (Attie et al, 2001, of record) teach methods of conjugating the proteins GH and/or IGF-I at one or two cysteine residues with monomethyl-PEG of between about 5000 Daltons to about 40000 Daltons to improve the circulating half-like for these proteins and administering such IGF-I conjugates with a IGFBP-4 polypeptide (e.g., column 13).

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brad Duffy whose telephone number is (571) 272-9935.

The examiner can normally be reached on Monday through Friday 7:00 AM to 4:30 PM, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Respectfully,
Brad Duffy
571-272-9935

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

/bd/
Examiner, Art Unit 1643
October 27, 2008